



Aerobic exercise and respiratory muscle strength in patients with cystic fibrosis

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Received 19 September 2012; accepted 20 January 2013

Available online 26 February 2013

KEYWORDS

Cystic fibrosis;
Exercise;
Respiratory muscle
strength;
Pressure-time index
of the respiratory
muscles

Summary

Background: The beneficial role of exercise in maintaining health in patients with Cystic Fibrosis (CF) is well described. Few data exist on the effect of exercise on respiratory muscle function in patients with CF. Our objective was to compare respiratory muscle function indices in CF patients that regularly exercise with those CF patients that do not.

Methods: This cross-sectional study assessed nutrition, pulmonary function and respiratory muscle function in 37 CF patients that undertook regular aerobic exercise and in a control group matched for age and gender which consisted of 44 CF patients that did not undertake regular exercise. Respiratory muscle function in CF was assessed by maximal inspiratory pressure ($P_{i_{max}}$), maximal expiratory pressure ($P_{e_{max}}$) and pressure-time index of the respiratory muscles (PTI_{mus}).

Results: Median $P_{i_{max}}$ and $P_{e_{max}}$ were significantly higher in the exercise group compared to the control group (92 vs. 63 cmH₂O and 94 vs. 64 cmH₂O respectively). PTI_{mus} was significantly lower in the exercise group compared to the control group (0.089 vs. 0.121). Upper arm muscle area (UAMA) and mid-arm muscle circumference were significantly increased in the exercise group compared to the control group (2608 vs. 2178 mm² and 23 vs. 21 cm respectively). UAMA was significantly related to $P_{i_{max}}$ in the exercising group.

Conclusions: These results suggest that CF patients that undertake regular aerobic exercise maintain higher indices of respiratory muscle strength and lower PTI_{mus} values, while increased UAMA values in exercising patients highlight the importance of muscular competence in respiratory muscle function in this population.

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Introduction

In cystic fibrosis (CF) patients, cumulative pulmonary infections lead to a gradual decline in lung function while nutritional impairment is common.¹ Respiratory muscle function is affected by chronic obstructive pulmonary disease and chronic nutritional deficiency.²

Physical activity plays an important role in maintaining health in patients with CF.³ Regular aerobic exercise slows the rate of lung function decline,⁴ while exercise combined with physical therapy has been associated with a statistically significant increase in FEV₁ over physical therapy alone.⁵ Furthermore, exercise has been reported to increase peak aerobic capacity, level of activity and quality of life.⁶ A single exercise bout resulted in inhibition of epithelial sodium channels in patients with CF partially normalizing transepithelial potential difference,⁷ while progressive aerobic exercise resulted in increased recruitment in lung ventilation.⁸ Following a supervised three-month running conditioning program, CF patients exhibited increased ventilatory muscle endurance.⁹ CF patients subjected to high intensity exercise training did not develop overt low frequency fatigue of the respiratory muscles.¹⁰

Respiratory muscle strength can be assessed by measurement of maximal inspiratory pressure (P_{i,max}) and maximal expiratory pressure (P_{e,max}).¹¹ Respiratory muscle function can be evaluated by measurement of the non-invasive pressure-time index of the respiratory muscles (PTI_{mus}).¹² PTI_{mus} is a composite index of respiratory muscle efficiency that incorporates the mean inspiratory pressure developed by the inspiratory muscles during inspiration (P_{i,mean}) in relation to the maximal inspiratory pressure (P_{i,max}), and the duration of inspiration (Ti) in relation to the total time of respiration (Ttot).¹² Higher efficiency of the respiratory muscles is demonstrated by lower values of PTI_{mus}, while high PTI_{mus} values are related to increased risk of respiratory muscle fatigue.¹² To our knowledge, no data exist in the literature, relating exercise to respiratory muscle function assessed by measurement of PTI_{mus}.

Our hypothesis was that patients with CF who undertake regular aerobic exercise would exhibit improved respiratory muscle function compared to CF patients that do not undertake regular physical activity. The objective of this study was, therefore, to compare respiratory muscle function by measurement of P_{i,max}, P_{e,max} and PTI_{mus} between exercising and non-exercising CF patients with no gross hyperinflation, and investigate whether the weekly amount of time spent on aerobic exercise significantly relates to indices of respiratory muscle function.

Methods and materials

Study design

This was an observational cross-sectional study which constituted part of a trial investigating respiratory muscle function in patients with CF.

Subjects

CF patients attending their follow up appointments in the Department of Cystic Fibrosis of Aghia-Sophia Children's Hospital in Athens, Greece were eligible for the study. The diagnosis of CF was confirmed by abnormal sweat-test results and confirmed with expanded mutation analysis.¹³ Patients in acute exacerbation during the past month, patients on steroid treatment, patients with evidence of marked hyperinflation on chest radiography or computed tomography and patients with coexisting respiratory diseases were excluded from the study. Standard chest physical therapy was undertaken by all CF patients.

Measurements

Equipment

Airway flow was recorded with a pneumotachograph (Mercury F100L, GM Instruments, Kilwinning, Scotland) connected to a differential pressure transducer (DP45, range ± 3.5 cm H₂O, Validyne Corp, Northridge, CA, USA). Airway pressure (Paw) was measured from a side port on the pneumotachograph, which was connected to a differential pressure transducer (DP45, range ± 225 cm H₂O, Validyne Corp, Northridge, CA, USA). Amplification of the signals from the differential pressure transducers was performed by a carrier amplifier (Validyne CD 280, Validyne Corp, Northridge, CA, USA). Amplified signals were recorded and displayed in real time on a computer (Dell Optiplex GX620, Dell Inc., Texas, U.S.A) running Labview™ software (National Instruments, Austin, Texas, U.S.A) with analog-to-digital sampling at 100 Hz (16-bit NI PCI-6036E, National Instruments, Austin, Texas, U.S.A).

Measurement of respiratory pressures, breathing cycle components and lung function parameters

Airway pressure generated 100 ms after an occlusion (P_{0.1}), P_{i,max}, P_{e,max}, respiration rate (RR), tidal volume (TV), minute ventilation (MV), inspiratory time (Ti), total time of respiration (Ttot) and inspiratory time ratio (Ti/Ttot) were measured. P_{0.1} was calculated as the airway pressure generated 100 msec after an occlusion while the child/adult was quietly breathing. Five or more airway occlusions were performed and the average P_{0.1} value was calculated. P_{i,max} was measured from Residual Volume against an occluded airway upon a maximal inspiratory effort.¹⁴ P_{e,max} was measured from Total Lung Capacity against an occluded airway upon a maximal expiratory effort.¹⁴ P_{i,max} and P_{e,max} were measured on the basis of five maximal reproducible respiratory efforts and the maximum achieved value was recorded. A unidirectional valve (dead-space 8 ml) attached to the rubber mouthpiece was utilized to perform the occlusions. A small needle leak was incorporated in the respiratory circuit in order to avoid artificial glottic closure.¹¹ Care was taken to eliminate any leak around the mouthpiece. Only P_{i,max} and P_{e,max} maneuvers with plateau pressure of at least 1 s were accepted for subsequent analysis.¹¹ Forced expiratory volume in 1 s (FEV₁), Maximal Expiratory Flow between 25 and 75% of VC (MEF₂₅₋₇₅) and Forced vital capacity (FVC) were measured with a pneumotachograph using a Jager-Masterscreen Pulmonary

Function analyzer (Jager AG, Wurzburg, Germany). The pulmonary function tests were performed in accordance to European Respiratory Society guidelines¹⁵ and expressed as percentage of normal values (%predicted).^{16,17}

Calculation of PTImus

The pressure-time index of the inspiratory muscles (PTI_{mus}), was calculated as: $PTI_{mus} = (P_{i_{mean}}/P_{i_{max}}) \times (Ti/T_{tot})$, where $P_{i_{mean}}$ was the average airway pressure during inspiration, obtained from the formula $P_{i_{mean}} = 5 \times P_{0.1} \times Ti$, $P_{i_{max}}$ was the maximum inspiratory airway pressure, Ti was the inspiration time and T_{tot} was the total time for each breath, calculated from the airway flow signal.^{12,18,19}

Nutritional parameters

Body Mass Index (BMI) was calculated as the individual's body weight in kilograms divided by the square of his height in meters.¹⁷ For patients aged 6–19 years of age the BMI z-score method was used while patients older than 20 years, were evaluated with the BMI method.²⁰ Mid-arm muscle circumference (MAMC) was measured to the nearest centimeter, midway between the tip of the acromion and the olecranon process with the right hand hanging relaxed.²¹ Triceps Skinfold Thickness (TST) was measured to the nearest millimeter, halfway over the triceps muscle by a Harpenden Skinfold Caliper (Baty International, UK) and with the skinfold parallel to the longitudinal axis of the humerus.²¹ Upper Arm Muscle Area (UAMA) was derived and calculated from these indices.²²

Exercise

The nature and degree of physical activity was assessed by questionnaire. Patients that formed the exercise group engaged in moderate to vigorous aerobic physical activity at least three times a week over the past three months for forty-five minutes each time.^{9,23,24} Activities that were accepted as moderate to vigorous physical activity were cycling, running, swimming, football, basketball, volleyball, athletics, tennis, martial arts, gymnastics and rowing.^{23,25} Total training hours per week were calculated on the basis of the average training hours per week of the three previous consecutive weeks prior to the measurements. CF patients that did not participate in planned physical activity formed the control group.

Statistics

Data were assessed for normality using the Kolmogorov–Smirnov and Shapiro–Wilk tests. Differences between groups were checked for significance using the Mann–Whitney rank sum test. Linear regression analysis was used to examine the relation of PTI_{mus} , $P_{i_{max}}$ and Pe_{max} to total training hours per week and the relation of PTI_{mus} , $P_{i_{max}}$ and Pe_{max} to UAMA, BMI and BMI z-score. Variables without normal distribution were logarithmically transformed.

Statistical analysis was performed using SPSS 17.0 (SPSS Inc, Chicago IL, USA).

Ethics approval

The study protocol was approved by the Hospital Ethics Committee. Parents, legal guardians or patients provided informed written consent prior to the study.

Results

Between November 2009 and April 2010, 113 potentially eligible patients were evaluated. 32 patients were excluded according to the criteria described above. 81 patients were included in the study. The exercise group comprised of 37 CF patients while the control group consisted of 44 CF patients matched as possible for age and sex. Ages ranged from 7 to 34 years.

Anthropometric, nutrition, pulmonary function and respiratory muscle function data in the exercise and the control groups are presented in Table 1. The median value of exercise hours per week was 6 and the interquartile range 4–8. Exercise characteristics of the study population are presented in Table 2. Weight, height, BMI, BMI z-score and TST were not significantly different in the exercise compared to the control groups. MAMC and UAMA were significantly increased in the exercise group compared to the control group (Table 1).

FEV_1 , MEF_{25-75} and FVC did not exhibit significant difference between the two groups (Table 1). Breathing cycle components such as TV, TV/kg, TV/Ti, MV, RR, Ti, T_{tot} and Ti/T_{tot} were not significantly different between the two groups (Table 1).

$P_{i_{max}}$ and Pe_{max} (Fig. 1) were significantly increased while PTI_{mus} (Fig. 2) and $P_{i_{mean}}/P_{i_{max}}$, were marginally significantly decreased in the exercise group of patients compared to the control group (Table 1).

In the exercise group, there was a significant positive relation between UAMA and $P_{i_{max}}$ ($r = 0.356$, $p = 0.031$) but not between UAMA and Pe_{max} or PTI_{mus} . The number of total exercise hours per week was not found to be significantly related to any of $P_{i_{max}}$, Pe_{max} , PTI_{mus} , BMI z-score or UAMA.

Discussion

This study demonstrated that PTI_{mus} was significantly decreased and $P_{i_{max}}$ and Pe_{max} were significantly increased in exercising CF patients compared to non-regularly exercising CF patients. In the exercise group the amount of hours per week spent in exercise was not significantly related to the respiratory muscle indices examined.

The beneficial role of aerobic exercise in maintaining health in CF has been extensively reported in previous studies. A recent Cochrane review concluded that physical training has a positive effect on exercise capacity, strength and lung function.²⁶ Exercise improves transepithelial potential difference in the CF airway,⁷ improves mucus clearance,³ increases recruitment in lung ventilation⁸ and enhances airway clearance.²⁷ Aerobic capacity has been related to improved survival, quality of life and professional achievement in patients with CF.²⁸ Children with CF who regularly exercise, enjoy improved quality of life while

Table 1 Anthropometric, nutrition, pulmonary function and respiratory muscle function data in the exercise and the control groups.

	CF, N = 81		P value
	Exercise N = 37	Control N = 44	
Gender (male)	26 (70.3)	24 (54.5)	0.145**
Age (years)	14 (12–17)	13 (9–17)	0.085*
Weight (kg)	52 (38–62)	43 (31–60)	0.113*
Height (cm)	159 (145–170)	156 (130–166)	0.132*
BMI	22.0 (19.6–25.2) N = 5	21.0 (17.9–23.2) N = 8	0.464*
BMI z-score	0.04 (–0.61 to 0.66) N = 32	0.44 (–0.60 to 0.97) N = 36	0.559*
TST (mm)	11 (8–14)	12 (8–15)	0.575*
MAMC (cm)	23 (20–26)	21 (18–25)	0.042*
UAMA (mm ²)	2608 (2.119–4216)	2178 (1788–3241)	0.029*
FEV ₁ (% pred)	99.1 (75.8–118.1)	100.5 (77.0–100.6)	0.909*
MEF _{25–75} (% pred)	73.0 (49.4–100.2)	74.8 (42.0–103.9)	0.954*
FVC (% pred)	106.3 (92.3–117.1)	104.3 (83.3)	0.539*
RR	18 (15–22)	19 (15–23)	0.898*
Ti (sec)	1.48 (1.18–175)	1.51 (1.24–1.90)	0.722*
Ttot (sec)	3.32 (2.65–3.98)	3.22 (2.67–4.09)	0.936*
Ti/Ttot	0.44 (0.42–0.45)	0.45 (0.43–0.47)	0.129*
TV (L)	0.54 (0.39–0.70)	0.49 (0.37–0.63)	0.282*
TV/kg (ml/kg)	10.6 (8.9–13.9)	10.4 (8.2–16.5)	0.872*
TV/Ti (L/sec)	0.34 (0.28–0.49)	0.35 (0.26–0.42)	0.201*
MV (L/min)	9.66 (6.96–12.54)	9.14 (6.83–11.14)	0.345*
Pe _{max} (cmH ₂ O)	94 (66–120)	64 (46–83)	<0.001*
Pi _{max} (cmH ₂ O)	92 (79–108)	63 (51–86)	<0.001*
P _{0.1} (cmH ₂ O)	2.47 (1.96–3.79)	2.38 (1.58–3.22)	0.341*
Pi _{mean} (cmH ₂ O)	18.3 (13.3–26.5)	17.9 (12.7–25.2)	0.409*
Pi _{mean} /Pi _{max}	0.197 (0.139–0.298)	0.271 (0.194–0.362)	0.045*
PTI _{mus}	0.089 (0.064–0.126)	0.121 (0.090–0.159)	0.034*

*Mann–Whitney rank sum test, values are presented as median (interquartile range).

**Pearson Chi-square test, values are presented as numbers (percentage).

BMI: Body mass index, BMI z-score: Body mass index z-score, TST: Triceps skinfold thickness, MAMC: Mid-arm muscle circumference, UAMA: Upper arm muscle area, FEV₁: forced expiratory volume in 1 s, MEF_{25–75}: maximal expiratory flow between 25% and 75% of VC, FVC: Forced vital capacity, RR: Respiratory rate, T_i: inspiratory time, T_{tot}: Total time of respiration, TV: Tidal volume, TV/kg: Tidal volume per kilogram of body weight, TV/T_i: inspiratory flow, MV: Minute ventilation, Pe_{max}: Maximal expiratory pressure, Pi_{max}: Maximal inspiratory pressure, P_{0.1}: inspiratory pressure 100 msec after onset of inspiration, Pi_{mean}: Inspiratory pressure, PTI_{mus}: Pressure-time index of the respiratory muscles.

there are also cost-benefit implications since they require fewer resources for antibiotics.²⁹ Exercise recommendations include various aerobic activities 3–5 times per week for 20–45 min at intensity levels of 60–85% of maximum heart rate depending on the severity of CF lung disease.²⁵ Questionnaire-derived activity measurements are reliable and valid tools in assessing physical activity in children with CF while they also correlate to accelerometer measurements which are thought to describe more reliably an individual's aerobic condition.^{30,31}

PTI_{mus} was initially assessed as an index to describe inspiratory muscle function by Gaultier et al.,¹⁸ validated by Ramonatto et al.¹² while Hayot et al.¹⁹ and Hahn et al.³² applied it in CF patients. PTI_{mus} is a non-invasive, global respiratory muscle index, which does not overlook the possible effects exerted in respiration by accessory respiratory muscles. Our study reports similar PTI_{mus} values compared to previous studies of PTI_{mus} in CF patients.^{19,32} Maximal respiratory pressures are found to achieve similar

values in our study compared to previous studies in CF patients,^{33–35} given that our study included a fair number of younger children who exhibit lower maximal respiratory pressures.³⁶

Spontaneous breathing in healthy individuals is maintained by the balance between Pi_{mean} and Pi_{max}. Pi_{mean} describes the respiratory load and consists of the lung and chest wall elastic loads plus the resistive loads. Pi_{max} describes the neuromuscular competence and incorporates properties of respiratory muscle strength, central drive and neural and neuromuscular transmission.³⁷ The Pi_{mean}/Pi_{max} ratio, which describes the inspiratory muscle energy demands, was significantly lower in the exercise group of our study. Pi_{mean} was not significantly different between the exercise and control groups of CF patients in our study. Furthermore, parameters that relate to respiratory drive such as respiratory rate, inspiratory flow (TV/Ti) and P_{0.1} were also not found to achieve significant difference between the exercise and the control groups. It follows that

Table 2 Different types of physical activity undertaken by the CF patients that form the exercise group of the study. As some subjects are engaged in more than one activity the aggregation of the number of subjects participating in physical activity is bigger than the number of patients comprising the exercise group of the study.

Physical activity	N
Football	15
Basketball	8
Gymnastics	6
Martial arts	3
Cycling	2
Athletics	1
Rowing	1
Running	1
Swimming	1
Tennis	1
Volleyball	1

respiratory muscle function assessed by means of PTI_{mus} might be partially preserved in patients with CF who exercise mainly due to the beneficial effect of exercise on Pi_{max} . Thus, the ventilatory balance in CF might be relatively maintained in exercising CF patients by strengthening of the respiratory muscles and not by alleviation of the respiratory load. Our results are in agreement with Orenstein et al.,⁹ who evaluated respiratory muscle endurance in CF patients before and after a supervised three month running program. This study reported that respiratory muscle endurance, which was assessed by maximal sustained hyperpnea, was significantly increased after the conditioning period.

Since respiratory muscles are also skeletal muscles, the more they are exercised the bigger and stronger they are expected to become. This is not a surprising finding and it applies to any individual and not only to CF patients. It would have been interesting to demonstrate a beneficial effect of exercise on lung function but such a relationship

failed to emerge in our study since exercising and non-exercising patients did not have significant differences in lung function indices. A likely explanation for this is that pressures required for non-forced tidal breathing are noticeably lower than the ones generated during forced maneuvers. Nevertheless, increased PTI_{mus} values indicate an increased risk of respiratory muscle fatigue which might occur if and when the patient is forced to encounter increased respiratory workload such as during an acute exacerbation or an acute infection. In these situations mobilizing respiratory reserves and maintaining adequate ventilation in the context of a potentially impending respiratory fatigue and failure, might be of particular clinical interest.

The amount of time spent in aerobic activity expressed as total hours per week was not related to indices of respiratory muscle function. This might indicate that a minimum of three forty-five minute workouts per week of moderate to vigorous intensity is adequate to exert beneficiary effect on respiratory muscle strength, as no further benefit was exhibited for total training hours per week that exceeded this number.

With regards to lung function indices, in our study FEV_1 , MEF_{25-75} and FVC were not significantly decreased in CF patients who did not undertake regular exercise compared to exercising patients. This is in agreement with previous studies. Selvadurai et al. found no significant difference in pulmonary function indices after aerobic training compared to no physical training.⁶ Nevertheless, Moorcroft et al.³⁸ and Schneiderman-Walker et al.⁴ found that long term aerobic physical training resulted in a slower pulmonary function decline in the exercise group compared to the control group.

With regards to anthropometry and nutrition, there were no statistically significant differences in weight, height, BMI, BMI z-score and TST between the two groups. Of note, median body weight in exercising patients was 9 kg higher compared to the non-exercising ones. Clinically, this might reflect a possible better nutritional state in exercising patients or relative differences in body composition. MAMC and UAMA were significantly increased in the exercise group as compared to the control group. Furthermore, UAMA was found to have a significant positive relation to Pi_{max} in the exercising group. The association of UAMA to respiratory muscle indices has been reported in previous studies¹⁹ while respiratory muscle strength has been shown to be significantly related to limb muscle strength in patients with CF.³⁹ This probably demonstrates that reduced muscle mass in CF patients predisposes to reduced respiratory muscle strength.

This study has some limitations that need to be considered. Being a cross-sectional study it does not evaluate the effect of exercise on individual subjects over a predefined time-period. It is difficult to assess whether CF patients are more active because they are fitter or if they are fitter because they are more active. A longitudinal study might be better equipped on answering this point. Furthermore, information relating to physical activity was collected by questionnaire and the intensity and adherence to the exercise regimen was not universal or supervised. Thus, the definition and standardization of exercise is rather limited and restricts the strength of our conclusions. Unfortunately,

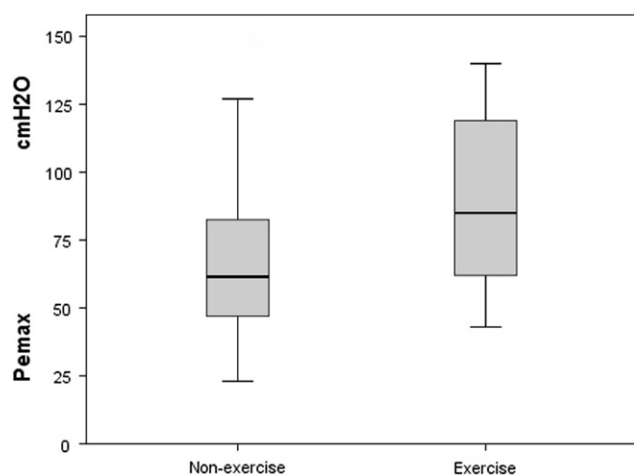


Figure 1 $P_{e_{max}}$ in exercising and non-exercising CF patients. Horizontal lines represent the 5th, 25th, 50th, 75th and 95th percentile of $P_{e_{max}}$ values.

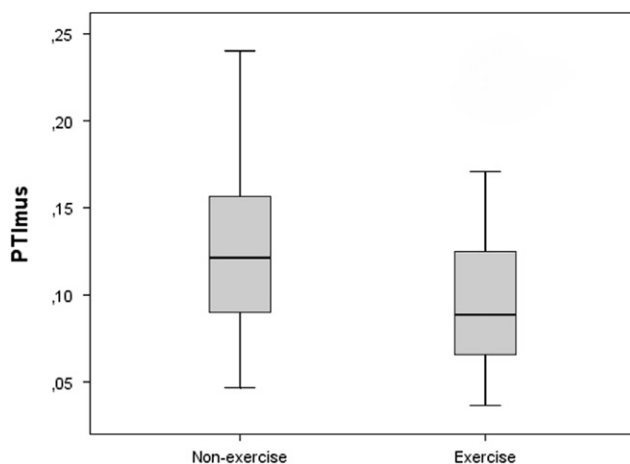


Figure 2 PTI_{mus} in exercising and non-exercising CF patients. Horizontal lines represent the 5th, 25th, 50th, 75th and 95th percentile of PTI_{mus} values.

very limited data are available assessing respiratory muscle function after predefined interventional exercise. Orenstein et al.⁹ investigated the effect of a supervised three-month running program on respiratory muscle endurance in CF patients and concluded that exercising subjects had significantly increased ventilatory muscle endurance, as evaluated by sustained hyperpnea scores. Inspiratory muscle training has resulted in improved respiratory muscle strength and endurance properties in patients with myasthenia gravis,⁴⁰ although this was a targeted respiratory muscle training regimen and not a form of aerobic sport activity. Overall, the population of CF patients incorporated in the study was in a good respiratory condition, as indicated by the median spirometric values, limiting thus the possibility of identifying parameters associated with poor respiratory muscle function. Admittedly, FEV_1 is a rather insensitive index in quantifying treatment effects in CF interventional trials. Novel measures of ventilation inhomogeneity like multiple breath washout (Lung Clearance Index) might be better correlated to respiratory muscle function than spirometry, as it is more frequently abnormal than spirometry in children with CF.⁴¹ Given these methodological limitations, our results still suggest that exercising CF patients would be more unlikely to succumb to respiratory fatigue if they were exposed to increased respiratory loads, compared to less active CF subjects.

In conclusion, this study demonstrated that maximal respiratory pressures are significantly higher and PTI_{mus} is significantly lower in exercising CF patients compared to non-regularly exercising CF patients. Respiratory muscle strength properties are significantly related to nutritional indices that describe skeletal muscular status such as UAMA in exercising CF patients. Regular aerobic exercise might exert significant benefits on respiratory muscle function in patients with CF.

Conflict of interest statement

None declared.

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